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Title: ATINEOPLASTIC EXTRACT FROM *ACHILLEA MILLEFOLIUM*

Group Art Unit:
Before the Examiner:

Box Application
Assistant Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL OF U.S. NATIONAL PHASE APPLICATION PURSUANT TO 35 U.S.C. §371 AND 37 C.F.R. §1.414

Hon. Assistant Commissioner for Patents:

Applicants hereby request entry into the U.S. national stage of the enclosed international application pursuant to 35 U.S.C. §371 AND 37 C.F.R. §1.414.

Enclosed please find the following documents.

1. International application number PCT/CA00/00949;
2. International search report;
3. International preliminary examination report and amended claims 1-5;
4. Fee calculation sheet;
5. Form PCT/IB/308;
6. Check in the amount of $1,040.00;
7. Return postcard.

Respectfully submitted,

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I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231
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ANTINEOPLASTIC EXTRACT FROM *ACHILLEA MILLEFOLIUM*

BACKGROUND OF THE INVENTION

(a) Field of the Invention

The invention relates to isolated and purified plant extracts, and more particularly to one from *Achillea millefolium* to treat and prevent neoplastic disorders.

(b) Description of Prior Art

Yarrow is an important member of the *Asteraceae* branch of the *Compositae*, the daisy family. Common names for yarrow include milfoil staunch weed, nosebleed, soldier's herb, carpenter's wort, thousand weed, woundwort, bloodwort boomadaran and knight's milfoil. There are about 100 different species of yarrow that grow mainly in temperate region of the world. Yarrow, or *Achillea millefolium*, is said to have been used by the Greek hero Achilles to stop the bleeding of his warrior's wounds.

Yarrow (*Achillea millefolium* LINNAEUS) is used as a medicinal plant in different parts of the world, as an haemostatic, emmenagogue, antipyretic and diaphoretic in cases of common cold.

An infusion is generally made from *Achillea millefolium*, which is also used for lack of appetite, cramps, flatulence and other stomach-related disorders. Aboriginal people and pioneers also used yarrow as a tea to treat digestive disorders and fevers and as a poultice to treat cuts and burns, and chewed the leaves to relieve toothache pain. Yarrow has long been associated with the healing of wounds and the steeming of blood flow. The existing literature indicates that yarrow improves colon and liver function, is good against anemia, liver disease, skin disease, eczema, liver, psoriasis and rashes, as well as for treating cold, flu, fever, hypertension, painful menstruation

and bleeding. The value of yarrow as an anti-spasmodic and diuretic agent, as well as an anti-inflammatory and antiseptic compound, has been demonstrated.

The use of yarrow tea against cancer is known. For example, in Iran, people have been using yarrow tea for cancer for several hundreds years. Yarrow tea has been used in different parts of the world for centuries without manifesting toxicity or side effects, and some cancer patients in the United States and Canada have been taking yarrow as an alternative medicine. However, no proven anticancer activity has been reported.

Antitumor sesquiterpenoids were recently identified and isolated as methyl esters from *Achillea millefolium*, namely achimillic acids A, B, and C,. These compounds are active against mouse P-388 leukemia cells *in vivo*.

Known constituents of yarrow are essential oils, namely cineol, proazulene and achilleine.

Neoplastic disorders such as cancer are treated with agents which are generally toxic with severe side-effects.

It would be highly desirable to be provided with a substantially pure biologically active fraction isolated from *Achillea millefolium* that would have an antineoplastic activity, and that could be used to treat or prevent diseases such as cancer.

SUMMARY OF THE INVENTION

One aim of the present invention is to provide purified biologically active fractions isolated from *Achillea millefolium* that may be used to treat or prevent disorders such as cancer.

In accordance with the present invention there is provided a substantially pure biologically active

extract isolated from *Achillea millefolium*, said extract having an antineoplastic activity.

In accordance with one embodiment of the present invention, the extract consists of a crude methanol extract.

In accordance with another embodiment of the present invention, there is provided the use of such an extract for the preparation of a medicament for the treatment and/or prevention of a neoplastic disorder, such as cancer.

In accordance with another embodiment of the present invention, there is provided an antineoplastic composition to treat and/or prevent cancer, said composition comprising a therapeutically effective amount of a substantially pure extract isolated from *Achillea millefolium* having antineoplastic activity, and a suitable carrier.

In accordance with another embodiment of the present invention, there is provided a method for treating and/or preventing a cancer in a patient, said method comprising administering to said patient a therapeutically effective amount of a substantially pure biologically active extract isolated from *Achillea millefolium* with a pharmaceutically acceptable carrier.

The composition may be administered to a patient susceptible of developing or suspected of having a cancer, in an amount efficient to treat or prevent the cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates the tracing obtained with the analytical HPLCs of the extracts;

Fig. 2 illustrates the fractions obtained with a large scale;

Fig. 3 illustrates a dose-response relationship for a methanol extract; and

Fig. 4 illustrates a dose-response relationship for fractions of methanol extracts.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided purified biologically active fractions isolated from *Achillea millefolium* to treat diseases such as cancer.

Fractions from *Achillea millefolium* LINNAEUS have been isolated. The purified fractions were administered to animals in which cancer was induced. No toxicity was observed at the doses administered. Moreover, the isolated organic soluble fractions have antimetastatic activity in a mouse cancer model. The isolated active fractions contain biologically active molecules that may be used to treat diseases including cancer.

More particularly, the crude methanol fraction had a good antimetastatic activity in the Lewis lung carcinoma model.

The animal model published by Tozyo et al. (*Chem Pharm Bull*, 1994, **42**:1096-1100) consists of a mouse leukemia P388 cell model. Tozyo et al. (supra) injected both cells and drugs intraperitoneally. This does not mimic physiological/pharmacological conditions observed in human cancer. Indeed, the conditions in Tozyo et al. resemble that of a petri dish where both the target and the drug are in direct contact. According to the present invention, the cells are injected subcutaneously to the Lewis lung carcinoma model. The cells then invade a distant site, such as lung, and form metastases. The test article is given by intraperitoneal route. Accordingly, the active

component(s) need to be absorbed, perhaps metabolized, before acting on primary tumors and/or metastases. This is closer to human disease in term of the growth versus multistep mechanisms of invasion.

As may be seen in Fig. 3, a dose-response relationship was observed.

As may be seen if Fig. 4, the E1, E2 and E4 fractions were the most active in inhibiting lung metastases.

Molecule(s) responsible for the biological activity of the extracts may be identified and characterized. The(se) molecule(s) may then be used to treat or prevent cancer, leukemias, as well as other diseases.

The fractions and molecules contained therein are advantageous over the whole plant or teas made from the plant.

The present invention will be more readily understood by referring to the following examples which are given to illustrate the invention rather than to limit its scope.

EXAMPLE I

Fractionation

Dried plant was grounded, and then stirred in methanol at 25°C for 48h. The resulting extract was filtered and treated with fresh methanol for another 48h. The combined extracts were filtered, evaporated and analyzed by HPLC. Analytical HPLC (Waters™ 600, Photodiodearray™ 996) was performed with two Whatman Partisil™ 10 ODS-2 analytical columns in series (4.6 x 250 mm). The gradient used consisted of 25-100% acetonitrile in water, 50 min gradient at a flow rate of 1 ml/min. Three fractions were identified according to retention times, namely the fractions 0-10, 11-22

and 23-60. The tracing of this analytical HPLC is shown in Fig. 1.

A large scale was then used. Briefly, 2 grams from methanol extract were dissolved in glass-distilled methanol and filtered, and three separations were performed with one Partisil™ 10 ODS-2 MAG-20 preparative column (22 x 500 mm) with the following gradient: 25-100% acetonitrile in water, 50 min. gradient at a flow rate of 18 ml/min. Four fractions were collected for each injection according to the following retention times: F1: 4.63-15.9; F2: 15.9-24.4; F3: 24.4-40.2; and F4: 40.2-60. The fractions are shown in Fig. 2.

The fractions were freshly solubilized in ethanol (final concentration is less than 20% of distilled water), and immediately used for *in vivo* studies or stored at -80°C.

EXAMPLE II

Lewis lung carcinoma (LLC) cell line and cell culture

The Lewis lung carcinoma (LLC) clone, M47, with a high metastatic potential to the lung, was established and characterized (Brodt P, *Cancer Res.*, **46**: 2442, 1986). These cells were confirmed free of mycoplasma infection. Cells were maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin, under 5% CO_2. Cells were passaged twice a week. Stocks of cells were generated and stored as early passages (passage no. 8-10 received as passage no. 1, was considered the initial stock). Cells were then propagated and stocks of the same passages were established and stored in liquid nitrogen for further experiments.

For tumor induction, cells were grown to 70% confluence in complete medium and then collected using

trypsin-EDTA solution [0.05% trypsin, 0.53 mM EDTA-4Na in HBSS without Ca^{++}, Mg^{++}, and $NaHCO_3$; Cellgro no. 25-052-Li]. Cells were then centrifuged and washed three times with phosphate buffer solution [D-PBS, Ca^{++} and Mg^{++} free; Cellgro no. 21-031-LV], and resuspended at a dilution of 0.1-1 x 10^6 cells/0.1 ml. Viability was examined by Trypan blue staining and only flasks in which the viability was >95% were used for *in vivo* studies.

The C57BL/10 mouse strain from the research laboratories and incinerators was used, and access to the animal facility is strictly limited to animal users. The animal room has two doors, one serving as the entrance and the other providing direct access to washing, sterilization and incineration facilities, which allows an accurate adjustment of environmental parameters including temperature, humidity, ventilation and lighting.

EXAMPLE III

Tumor cell inoculation and treatment

Five mice were housed per cage and fed a diet of animal chow and water *ad libitum*. After one week of acclimatization, LLC cells were transplanted subcutaneously, as a suspension of tumor cells (2-5 x 10^5 viable cells/0.1 ml) in the axillary region of the right flank. Animals were subjected daily to general examination. Tumor growth was monitored every second or third day using calipers. Tumor were measured along the longest axis (length) and the perpendicular shortest axis (width) and the relative tumor volume (in cm^3) was calculated by the formula: [Length (cm) x (width cm)2]/2. When the tumor reached a size of 0.5-1.0 cm^2 (in approximately 2-3 weeks), the mice were randomized into three groups.

In the first group, the mice were subjected to surgery to remove the primary tumor. The mice were lightly anesthetized with Forane. The skin overlying the tumor was cleaned with betadine and ethanol in a laminar flow hood. A small skin incision (0.5-1.0 cm) was made using a sterile scalpel and the tumor was carefully separated from the normal tissues (skin and muscle). LLC (at an early stage of growth; 1-3 weeks) is a well-localized tumor, and separation was easy to achieve without any significant damage to normal tissues. The tumor was removed, weighed and fixed for histopathology purposes. The wound was closed with surgical stainless steel clips (Autoclips™; 9 mm; Clay Adams, Inc., Parsippany, NJ). The site was further disinfected with Betadine™ and the animal was housed as described earlier.

In the second group, the mice were randomized after surgery into groups of 5 per cage. The cages were randomly assigned to specific experimental groups. The mice were then labeled by numbers using the "ear punching" method. Mice were checked daily to ensure the absence of infection. Animals with disconfort were sacrified immediately. An additional extra-group of control mice was included to determine the optimal timing for sacrifice in order to obtain a significant number of well localized lung metastases. The second group was subjected to the same experimental procedure as the first group, with the exception of drug treatment. Based on the second group, a period of two weeks after removal of the primary tumor was sufficient to obtain an average of 20-30 nodules on the lung surface. Therefore, a two-week period after primary tumor removal was used to sacrify treated mice.

EXAMPLE IV

Dosing schedule and treatment

Drugs were given by intraperitoneal (ip) route (0.5 ml per animal) in daily administration after tumor cell inoculation. Control animals were given the same volume of saline solution (0.9% sodium chloride; Abott Laboratories, lot no. 12 455 WS). The dose of each drug was normalized to an average of 20 g/body weight/per animal. The schedules for drug treatment were based upon conditions described in Figs. 3-4.

EXAMPLE V

Animal sacrifice, tumor/organs preparation

At the end of each experiment, for a total of 5-8 weeks, animals were sacrified in a CO_2 chamber and autopsied. Tumors, organs or both were removed under sterile conditions using a laminar flow hood. Tumors were weighed. Organs (5/group) were examined for gross pathological changes and then fixed in 10% formalin. Lungs were fixed in 10% Bouin's fixative diluted in a formalin solution, and lung surface metastases were counted using a stereomicroscope at 4x magnification or a magnifying-glass.

EXAMPLE VI

Statistical analysis

The umpaired Student t-test was used to compare statistical significance among various groups.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following,

in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A substantially pure biologically active extract isolated from *Achillea millefolium*, said extract having an anti-tumorogenic and anti-metastatic activity.

2. An extract according to claim 1, said extract consisting of a crude methanol extract.

3. The use of an extract according to claim 2, for the preparation of a medicament for the treatment and/or prevention of a malignant tumor and/or metastases thereof.

4. An anti-tumorogenic and anti-metastatic composition to treat and/or prevent malignant tumor and/or metastases thereof, said composition comprising a therapeutically effective amount of a substantially pure extract isolated from *Achillea millefolium* having antineoplastic activity, and a suitable carrier.

5. A method for treating and/or preventing a malignant tumor and/or metastases thereof in a patient, said method comprising administering to said patient a therapeutically effective amount of a substantially pure biologically active extract isolated from *Achillea millefolium* with a pharmaceutically acceptable carrier.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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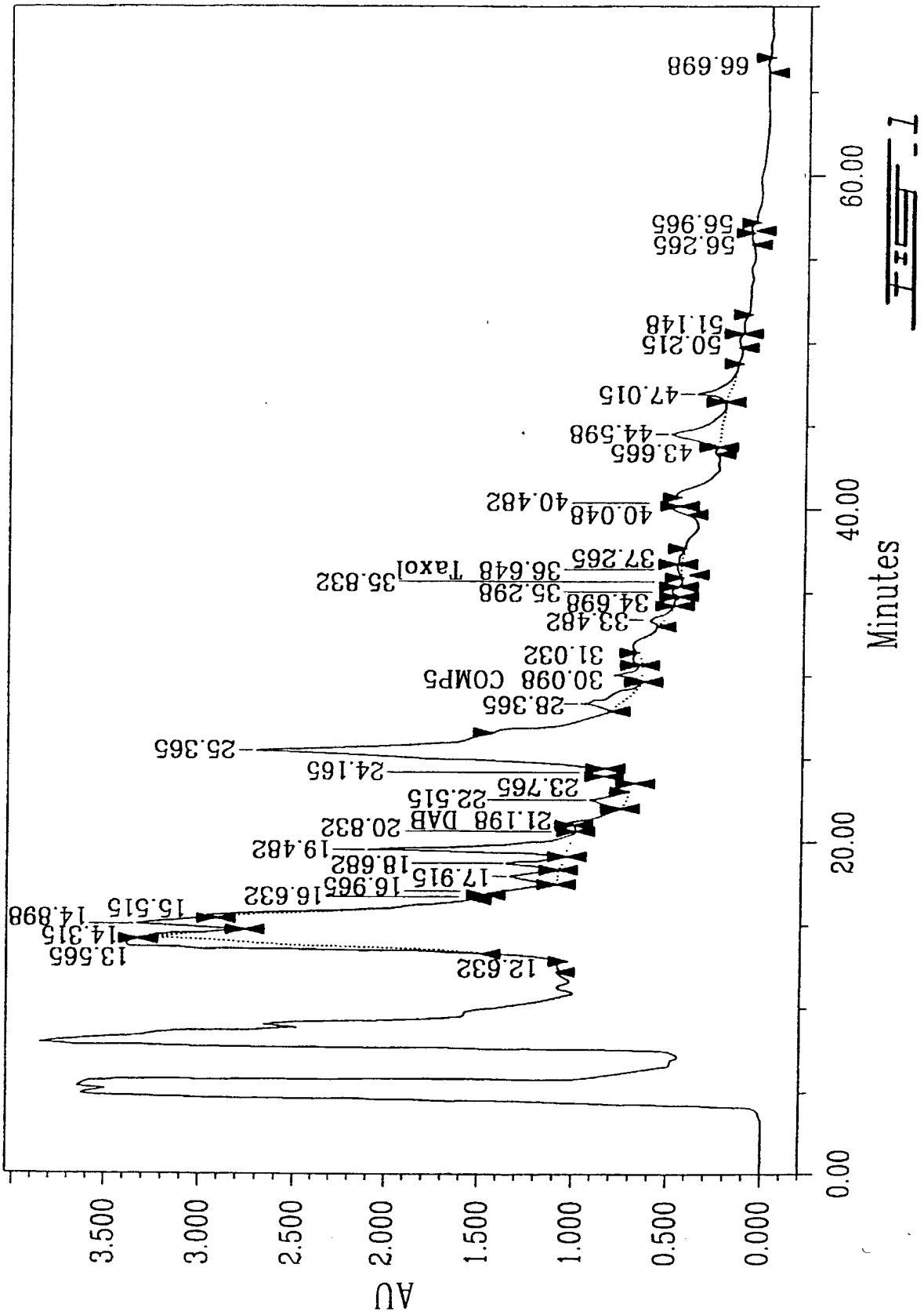
Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTINEOPLASTIC EXTRACT FROM *ACHILLEA MILLEFOLIUM*

(57) Abstract: The present invention relates to isolated and purified plant extracts. There is provided an isolated and purified extract from *Achillea millefolium* to treat and prevent cancer. The purified fractions were administered to animals in which cancer was induced. The fractions demonstrated antimetastatic activity. Molecules contained in the fractions may also be used to treat and prevent cancer.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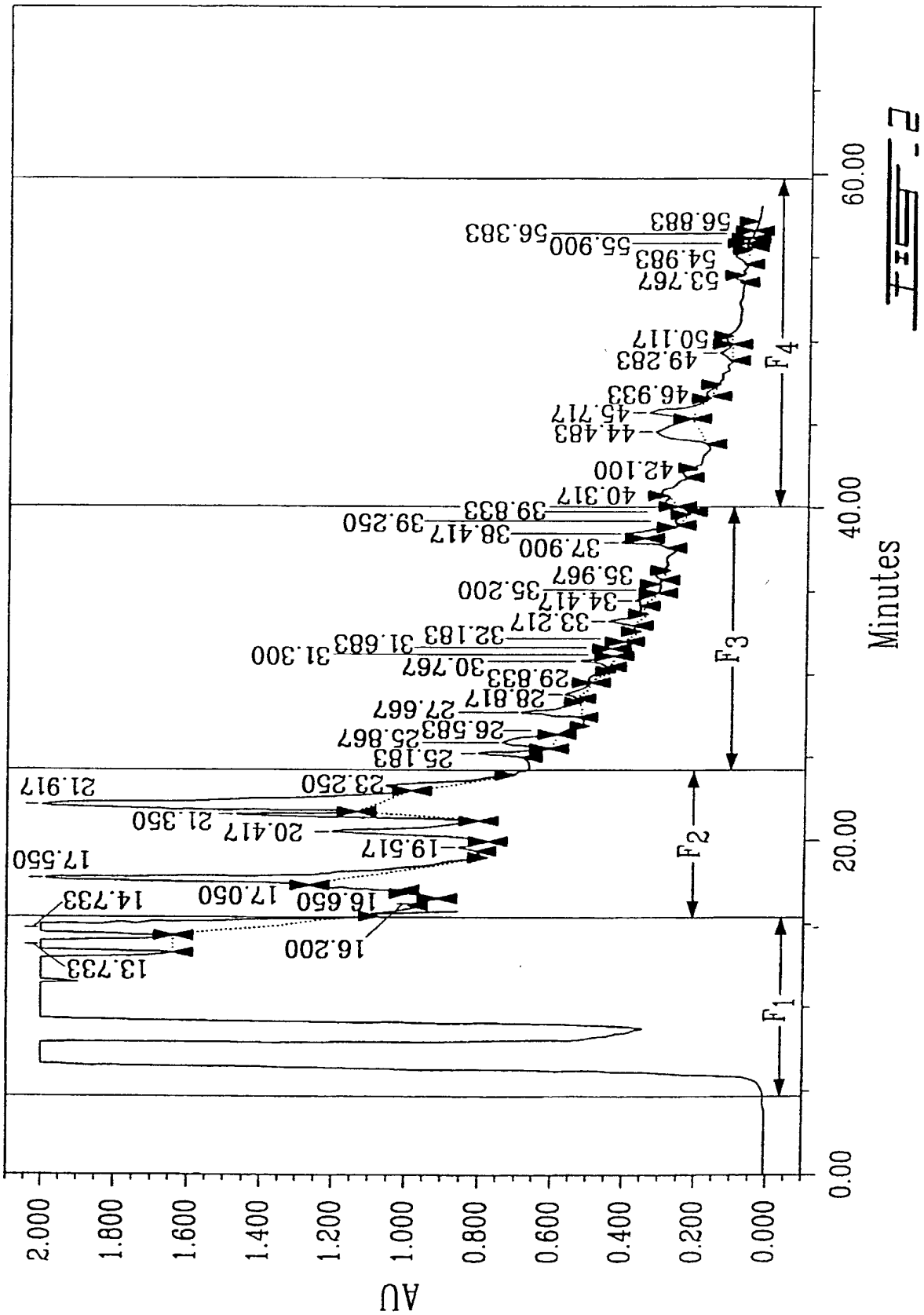
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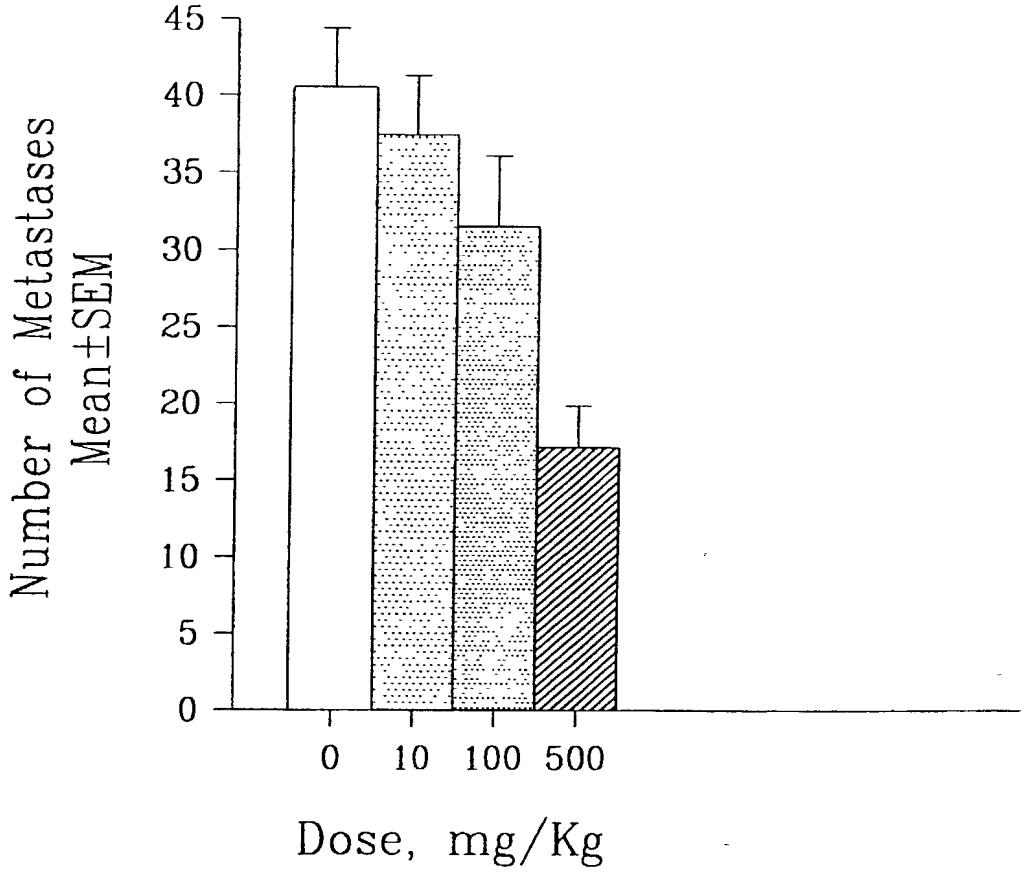
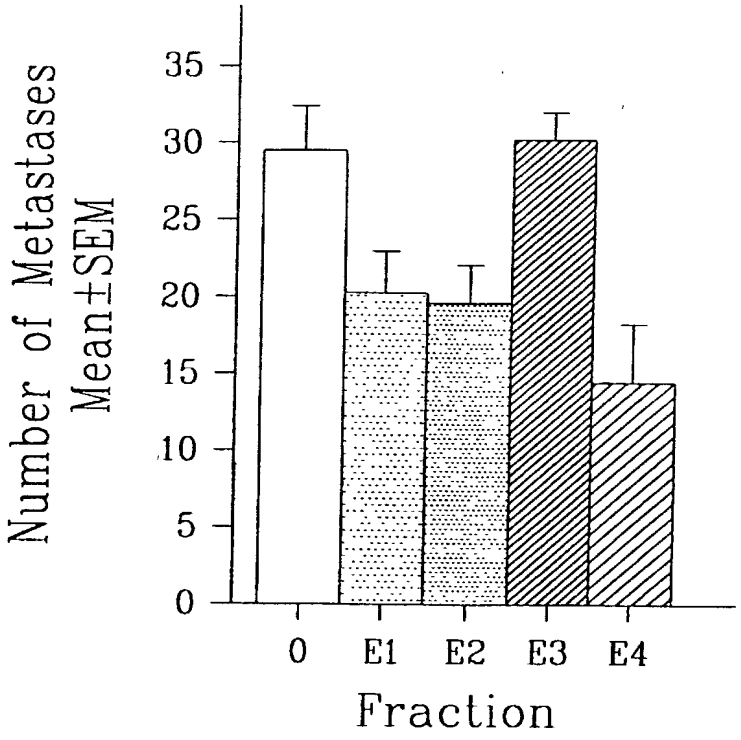
FIG. 2



7 ip administrations every second day
For each group n=10
No drug-related death was observed

Fig 3



E1: 100mg/Kg, 7 ip administrations every second day
E2: 100mg/Kg, 7 ip administrations every second day
E3: 100mg/Kg, 7 ip administrations every second day
E4: 100mg/Kg, 7 ip administrations every second day

ip = intraperitoneal
For each group n=6
No drug-related death was observed

Fig 4

PTO/SB/01 (10-01)

COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63) AND POWER OF ATTORNEY		
☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16(e)) required)	**Attorney Docket Number**	**SWA-002(1011/003)**
	First Named Inventor	**M. Alaoui-Jamali et al.**
	Complete if known	
	Application Number	
	Filing Date	
	Group Art Unit	
	Examiner Name	

As a below named inventor, I hereby declare that:

My residence, mailing address and citizenship are as stated below next to my name.

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ANTINEOPLASTIC EXTRACT FROM ACHILLEA MILLEFOLIUM

the specification of which

☐ is attached hereto.

OR

☒ was filed on _____ (mm/dd/yyyy)

as United States Application Number or PCT International Application Number **PCT/Ca00/00949**

and was amended on _____ (mm/dd/yyyy) (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	
60/149,697	**08/20/1999**	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63) AND POWER OF ATTORNEY

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*
PCT/CA00/00949	08/17/2000	

☐ Additional U.S. or PCT International application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent Trademark Office connected therewith:

☐ Customer Number

OR ☐ Registered practitioner(s) name/registration number listed below

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of sole or First Inventor:

☐ A petition has been filed for this unsigned inventor

1-00

Given Name (first and middle [if any])	Family Name or Surname
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Inventor's Signature _____ Date _____

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☒ Additional inventors are being named on the supplemental Additional Inventor(s) PTO/SB/02A attached hereto.

10/049492 .07 1502

COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63) AND POWER OF ATTORNEY

PTO/SB/02A (10-00)

DECLARATION	**ADDITIONAL INVENTOR(S) Supplemental Sheet Page 1 of 1**

2-00

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☐ A petition has been filed for this unsigned inventor

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Inventor's Signature Date

Residence:
City State Country Citizenship

Post Office Address

City Province or State Postal Code Or Zip Country

Name of Additional Joint Inventor, if any:

☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]) | Family Name or Surname

Inventor's Signature Date

Residence:
City State Country Citizenship

Post Office Address

City Province or State Postal Code Or Zip Country

☐ Additional inventors are being named on the supplemental Additional Inventor(s) PTO/SB/02A attached hereto.